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PATENT SPECIFICATION

NO DRAWINGS

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888,965

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International Classification:—C07c. A61k.

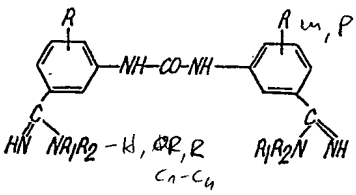
COMPLETE SPECIFICATION

Improvements in or relating to Diamidines

We, MAY & BAKER LIMITED, a British Company, of Dagenham, Essex, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new diamidines of therapeutic utility, to processes for their preparation, and to pharmaceutical compositions containing them.

The new diamidines of the present invention are the bases conforming to the general formula:

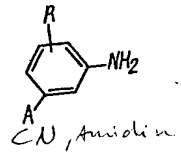


I

(wherein R is *meta* or *para* to the amidino group and represents a hydrogen or halogen atom, or a lower alkoxy group, and R_1 and R_2 are the same or different each representing a hydrogen atom or a lower alkyl group) and their acid addition salts. The word "lower" as applied herein to alkyl and alkoxy groups means that the group in question contains not more than four carbon atoms.

These new diamidines are useful in the treatment of protozoal diseases, especially babesiasis. In this regard it is known that 4,4¹-diamidinodiphenylurea exhibits slight activity against veterinary trypanosomiasis (Fulton and Yorke, Ann. Trop. med. parasit, 1942, *36*, 131) but it is completely inactive against *B. rodhaini* in mice. The diamidines of the present invention have high activity against *B. rodhaini* in mice and *B. bovis* in calves, an activity which is, therefore, completely unexpected. Compounds which possess this activity to an outstanding degree are those in which each symbol R represents a hydrogen atom; in particular, 3,3¹-diamidinodiphenylurea and 3,3¹-di(N-methylamidino)diphenylurea. The compounds of the invention are, furthermore, quick acting and of low toxicity.

According to a feature of the invention, the compounds of general formula I are prepared by a process which comprises reacting a compound of the general formula:



II

(wherein R is as hereinbefore defined, and A is a cyano group or an amidino group of the formula $-C(:NH)NR_1R_2$ in which R_1 and R_2 are as hereinbefore defined), or an acid addition salt thereof, with phosgene or 3,5-dimethylpyrazole-1-carbonamide and, where A represents a cyano group, converting the cyano group into an amidino group of formula $-C(:NH)NR_1R_2$ by known methods. By the expression "known methods" as used in this specification and accompanying claims is meant methods heretofore employed or described in the chemical literature.

In the aforesaid process when phosgene is a reactant and A in the reactant of formula II is (a) a cyano group, the reaction is preferably carried out in the presence of an acid binding agent such as pyridine and in an inert solvent or (b) an amidino group $-C(:NH)NR_1R_2$, the reaction is preferably effected either in a basic solvent such as pyridine or in an inert solvent in the presence of an acid binding agent, such as an alkali metal carbonate, bicarbonate or acetate, using

the amidine in the form of an acid addition salt, e.g. hydrochloride.

In the aforesaid process when 3,5 - dimethylpyrazole - 1 - carbonamide is a reactant, the reaction is preferably effected at an elevated temperature in a hydroxylic solvent such as 2 - ethoxyethanol.

Conversion of the cyano group in a resultant product into an amidino group $-C(:NH)NR_1R_2$ may be effected by known methods, for example, by successive treatment with hydrogen chloride and ammonia or an amine conforming to the formula R_1R_2NH (wherein R_1 and R_2 are as hereinbefore defined).

According to a further feature of the invention the diamidines of general formula I in which either or both of R_1 and R_2 represent lower alkyl groups are prepared by alkylating a corresponding compound in which R_1 and R_2 represent hydrogen atoms by known methods for the alkylation of amidines, for example, by reaction with alkyl halides, sulphates or toluene - *p* - sulphonates.

For therapeutic purposes the bases of the present invention will normally be administered in the form of one of their acid addition salts, it being understood that only those such salts should in practice be employed as contain anions that are relatively innocuous to the animal organism when used in therapeutic doses so that the beneficial physiological properties inherent in the parent compound are not vitiated by side-effects ascribable to those anions. Suitable salts include hydrohalides, for example, hydrochlorides, isethionates, 8 - chlorotheophyllinates, phosphates, nitrates, sulphates, maleates, fumarates, citrates, tartrates, methane sulphonates and ethane disulphonates. The hydrohalides and isethionates are salts which are preferred.

The following Examples illustrate the invention.

EXAMPLE I

m - Aminobenzonitrile (50 g.) in anhydrous pyridine (200 ml.) was treated with a solution of phosgene (15 ml.) in anhydrous toluene (100 ml.) over 10 minutes with mechanical stirring. The red solution was heated for 0.5 hour on the steam bath, cooled, and added to water (2 litres). The pale grey precipitate was filtered off, washed with ether, and crystallised from methanol (250 ml.). N,N^1 - Di(*m* - cyanophenyl)urea separated as grey prisms, m.p. 205—206°C.

A suspension of N,N^1 - di(*m* - cyanophenyl)urea (42 g.) in anhydrous chloroform (420 ml.), containing anhydrous ethanol (70 ml.), was saturated with anhydrous hydrogen chloride at 0—5°C. After setting aside for 2 hours, a clear solution was obtained, which began to crystallise. After a week, the crystals were filtered off, washed well with anhydrous ether, and dried over calcium chloride. The iminoether hydrochloride so obtained (72 g.) was added to saturated anhydrous ethanolic ammonia (720 ml.), and the suspension heated at 55—60°C. for 6 hours. Solution was obtained after an hour, followed by crystallisation of the product. After cooling to 20°C. the crystals were filtered off, and recrystallised from 2N hydrochloric acid (300 ml.). 3,3^1 - Diamidinodiphenylurea dihydrochloride monohydrate separated as white prisms, m.p. 286°C. (decomp.).

EXAMPLE II

Anhydrous hydrogen chloride was passed into a mechanically stirred fine suspension of N,N^1 - di(*m* - cyanophenyl)urea (55 g.) (prepared as described in Example I), anhydrous chloroform (550 ml.) and anhydrous ethanol (91.5 ml.) at 0—5°C. The saturated solution was set aside at room temperature, crystallisation commencing after a few hours. After 5 days, the iminoether hydrochloride formed was filtered off, washed with anhydrous ether, and dried over calcium chloride. The crystals (90 g.) were dissolved in ice-water (900 ml.) and the solution was basified at 0—10°C. with 2N sodium hydroxide in the presence of chloroform (500 ml.). The chloroform extract was separated, mixed with a chloroform wash of the alkaline liquor, washed with saturated brine, and dried over anhydrous sodium sulphate. After filtering off the drying agent, the solution was concentrated at 15—25 mm. from a bath at 35—40°C., and the residual gum (79.2 g.) dissolved in ethanol (792 ml.). Ammonium isethionate (60 g.) in water (120 ml.) was added and the solution was heated in a bath at 60°C. for 8 hours. Crystallisation occurred during the later stages of the reaction. The reaction mixture was cooled to 5°C., and the crystals were filtered off, washed with acetone and dried at 90°C. Crystallisation from methanol-acetone gave 3,3^1 - diamidinodiphenylurea diisethionate as white needles, m.p. 209°C., the melt decomposing at 256°C.

EXAMPLE III

A fine suspension of *m* - aminobenzamidine monohydrochloride (3.65 g.) in anhydrous pyridine (15 ml.) was treated at 5—10°C. with a solution of phosgene (0.75 ml.) in anhydrous toluene (5 ml.). The reaction mixture was heated on a steam bath for half an hour, cooled to 25°C., and the liquor decanted. Treatment of the residual gum with ethanol and ether yielded a sticky solid. Two crystallisations from 2N hydrochloric acid gave 3,3^1 - diamidinodiphenylurea dihydrochloride sesquihydrate, decomposing at 286°C.

EXAMPLE IV

A solution of *m* - aminobenzamidine monohydrochloride (3.45 g.) and 3:5 - dimethylpyrazole - 1 - carbonamide (1.4 g.) (Scott, O'Donovan, Kennedy and Reilly, J. Org. Chem., 1957, 22, 821) in β-ethoxyethanol (7 ml.) was refluxed for 5 hours. After cooling to 25°C., the solid which had separated

during the reaction was filtered off, washed with acetone, and dried at 50°C. Crystallisation from 2N hydrochloric acid gave 3,3¹ - diamidinodiphenylurea dihydrochloride sesquihydrate, decomposing at 286°C.

EXAMPLE V

Proceeding as described in Example I 3 - amino - 4 - methoxybenzonitrile (Blanksma and Petri, Rec. trav. chim., 1947, *66*, 365) was reacted with phosgene to give N,N¹ - di(3 - cyano - 6 - methoxyphenyl)urea as pale yellow needles, m.p. 315—316°C., which was converted by the procedure described in Example I to 3,3¹ - diamidino - 6,6¹ - dimethoxydiphenylurea dihydrochloride monohydrate as white needles from N hydrochloric acid, decomposing at 285—286°C.

EXAMPLE VI

Proceeding as described in Example I 3 - amino - 4 - chlorobenzonitrile was reacted with phosgene to give N,N¹ - di(6 - chloro - 3 - cyanophenyl)urea as white needles from dimethylformamide (decomposing at 330°C.) which was converted by the procedure described in Example I to 3,3¹ - diamidino - 6,6¹ - dichlorodiphenylurea dihydrochloride monohydrate as white prisms from 2N hydrochloric acid, decomposing at 280—282°C.

The 3 - amino - 4 - chlorobenzonitrile used as starting material was prepared as follows:—

Reduced iron (25 g.) was added slowly to a boiling solution of 4 - chloro - 3 - nitrobenzonitrile (25 g.) (Le Fevre and Turner, J. Chem. Soc. 1927, 1118) in 50% v/v acetic acid (380 ml.). After the vigorous reaction had subsided, the reaction mixture was heated on the steam bath for 15 minutes, and filtered hot. The residue was extracted with boiling 50% v/v acetic acid (2 × 100 ml.) and the combined filtrate and extracts were added to water (200 ml.). After cooling to 5°C., the precipitate was filtered off, washed with 2N acetic acid and water. Crystallisation from aqueous ethanol gave 3 - amino - 4 - chloro - benzonitrile as white needles, m.p. 93—94°C.

EXAMPLE VII

A suspension of N,N¹ - di(*m* - cyanophenyl)-urea (11.6 g.) (prepared as described in Example I) in anhydrous chloroform (116 ml.) containing anhydrous ethanol (19.4 ml.) was saturated with anhydrous hydrogen chloride at 0—5°C. After setting aside for 2 hours a clear solution was obtained, which began to crystallise. After a week, the crystals were filtered off, washed well with anhydrous ether, and dried over calcium chloride. The iminoether hydrochloride so obtained (20 g.) was dissolved in water (200 ml.) and the solution was basified at 0—10°C. with 2N sodium hydroxide. The base which separated was extracted with chloroform, and the chloroform extracts were mixed and dried over anhydrous sodium sulphate. After filtration from the drying agent, the chloroform was distilled off from a bath at 30—35°C. under reduced pressure. The residual gum (16.9 g.) was dissolved in anhydrous ethanol (200 ml.) and methylamine hydrochloride (6.6 g.) added. The solution was heated at 55—60°C. for 8 hours, and then concentrated under reduced pressure. 3N Hydrochloric acid (300 ml.) was added to the residual gum, and the mixture heated to solution. On cooling, 3,3¹ - di-(N - methylamidino)diphenylurea dihydrochloride sesquihydrate separated as white needles which decomposed from 210°C., finally melting at 273—274°C.

Similarly prepared were:

3,3¹ - Di(N - ethylamidino)diphenylurea dihydrobromide monohydrate, decomposing at 302—305°C.;

3,3¹ - Di(N,N - dimethylamidino)diphenylurea dihydrobromide hydrate, decomposing at 300—302°C.

The present invention includes within its scope pharmaceutical compositions comprising one or more of the compounds of formula I, or an acid addition salt thereof, and a significant amount of a pharmaceutical carrier which may be either a solid material or a liquid. In clinical or veterinary practice the compounds of the present invention will normally be administered by intramuscular injection in consequence of which the preferred formulations are those of the kind suitable for parenteral administration.

Preparations for parenteral administration are preferably in the form of sterile solutions in water of readily soluble salts. However, sterile solution in other suitable solvent media can be employed as also may sterile suspensions of sparingly soluble salts in water, oil or other inert solvents such as propylene glycol, with or without the addition of soluble or insoluble diluents and/or solid or liquid excipients.

Preparations for oral ingestion can be liquids or solids or any combination of these forms, such as solutions, suspensions, syrups, elixirs, emulsions, powders or tablets. Pharmaceutical preparations for administration of the active therapeutic agents in unit dose form can take the form of compressed powders (or tablets) or of a powder enclosed in a suitable capsule of absorbable material such as gelatin. These compressed powders (or tablets) can take the form of the active materials admixed with suitable excipients and/or diluents such as starch, lactose, stearic acid, magnesium stearate or dextrin.

In yet a further embodiment, the active material may, as such or in the form of a diluted composition, be put up in powder packets and employed as such.

The percentage of active ingredient in the compositions of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. Obviously several unit dosage

12. A modification of the process claimed in claim 7 for the preparation of diamidines conforming to the general formula in which either or both of R_1 and R_2 is a lower alkyl group which comprises alkylating a corresponding compound in which R_1 and R_2 represent hydrogen atoms by known methods for the alkylation of diamidines.

13. Process for the preparation of diamidines claimed in claim 1 substantially as described in any one of Examples I to VII.

14. Diamidines when prepared by the process claimed in any one of claims 7 to 13.

15. Pharmaceutical compositions comprising one or more diamidines as claimed in any one of claims 1 to 6 together with a significant amount of a pharmaceutical carrier.

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PROVISIONAL SPECIFICATION

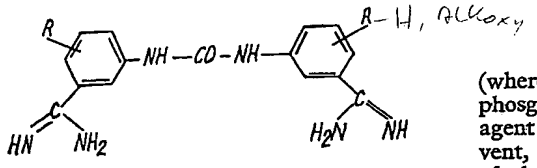
No. 40428 A.D. 1958

Improvements in or relating to Diamidines

We, MAY & BAKER LIMITED, a British Company, of Dagenham, Essex, do hereby declare this invention to be described in the following statement:—

This invention relates to new chemical compounds and in particular to new diamidines of therapeutic utility, to processes for their preparation, and to pharmaceutical compositions containing them.

The new diamidines of the present invention are the bases conforming to the general formula:

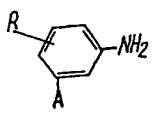


I

and their acid addition salts (wherein R represents a hydrogen atom or a substituent, *meta* or *para* to the amidino group, such as a halogen atom or an alkoxy group).

The compounds of general formula I are useful in the treatment of protozoal diseases, especially babesiasis. In this regard it is known that 4:4¹ - diamidinophenylurea exhibits slight activity against veterinary trypanosomiasis (Fulton and Yorke, Ann. Trop. med. parasit. 1942, *36*, 131) but it is completely inactive against *B. rodhaini* in mice. The high activity of 3:3¹ - diamidinodiphenylurea, the preferred compound of the invention, against *B. rodhaini* in mice and *B. bovis* in calves is, therefore, completely unexpected. Furthermore, the compounds of the invention are quick acting and of low toxicity.

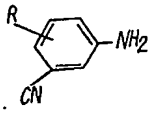
According to a feature of the invention, the compounds of general formula I are prepared by a process which comprises the interaction of a compound of the general formula:



II

(wherein A is a cyano or amidino group and R is as hereinbefore defined) or a salt thereof, with phosgene. Where A represents a cyano group, the said cyano group is subsequently converted into an amidino group by known methods.

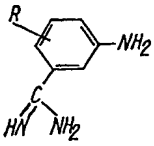
The reaction is preferably carried out by reacting a *m* - aminobenzonitrile of the formula:



III

(wherein R is as hereinbefore defined) with phosgene in the presence of an acid binding agent such as pyridine and in an inert solvent, such as toluene, followed by conversion of the dicyano compound thus obtained into the corresponding diamidine of general formula I by successive treatments with hydrogen chloride and ammonia.

In another preferred embodiment the reaction is carried out by reacting salt, such as the hydrochloride, or a *m* - aminobenzamidine of the general formula:



IV

(wherein R is as hereinbefore defined) with phosgene, either in a basic solvent such as pyridine, or in an inert solvent in the presence of an acid-binding agent such as an alkali metal carbonate, bicarbonate or acetate.

In veterinary practice the compounds of the present invention will normally be administered in the form of one of their acid addition salts, it being understood that only those such salts should in practice be employed as contain anions that are relatively innocuous to the animal organism when used in therapeutic doses so that the beneficial physiological properties inherent in the parent compound are

not vitiated by side-effects ascribable to those anions. Suitable salts include hydrohalides, for example, hydrochlorides, 8 - chlorotheophyllinates, phosphates, nitrates, sulphates, maleates, fumarates, citrates, tartrates, methane sulphonates and ethane disulphonates.

The following Example illustrates the invention.

EXAMPLE I

m - Aminobenzonitrile (50 g.) in anhydrous pyridine (200 ml.) was treated with a solution of phosgene (15 ml.) in anhydrous toluene (100 ml.) over 10 minutes with mechanical stirring. The red solution was heated for 0.5 hour on the steam bath, cooled, and added to water (2 litres). The pale grey precipitate was filtered off, washed with ether, and crystallised from ethanol (250 ml.). N:N^1 - Di(*m* - cyanophenyl)urea separated as grey prisms, m.p. 205—206°C.

A suspension of N:N^1 - di(*m* - cyanophenyl)urea (42 g.) in anhydrous chloroform (420 ml.), containing anhydrous ethanol (70 ml.), was saturated with anhydrous hydrogen chloride at 0—5°C. After setting aside for 2 hours, a clear solution was obtained, which began to crystallise. After a week, the crystals were filtered off, washed well with anhydrous ether, and dried over calcium chloride. The iminoether hydrochloride so obtained (72 g.) was added to saturated anhydrous ethanolic ammonia (720 ml.), and the suspension heated at 55—60°C. for 6 hours. Solution was obtained after an hour, followed by crystallisation of the product. After cooling to 20°C. the crystals were filtered off, and recrystallised from 2N hydrochloric acid (300 ml.). 3:3^1 - Diamidinodiphenylurea dihydrochloride monohydrate separated as white prisms, m.p. 286°C. (decomp.).

The present invention includes within its scope pharmaceutical compositions comprising one or more of the compounds of formula I, or an acid addition salt thereof, and a significant amount of a pharmaceutical carrier which may be either a solid material or a liquid. In clinical practice the compounds of the present invention will normally be administered by injection in consequence of which the preferred formulations are those of the kind suitable for parenteral administration.

Preparations for oral ingestion can be liquids or solids or any combination of these forms, such as solutions, suspensions, syrups, elixirs, emulsions, powders or tablets. Pharmaceutical preparations for administration of the active therapeutic agents in unit dose form can take the form of compressed powders (or tablets) or of a powder enclosed in a suitable capsule of absorbable material such as gelatin. These compressed powders (or tablets) can take the form of the active materials admixed with suitable excipients and/or diluents such as starch, lactose, stearic acid, magnesium stearate or dextrin.

In yet a further embodiment, the active material may, as such or in the form of a diluted composition, be put up in powder packets and employed as such.

Preparations for parenteral administration are preferably in the form of sterile solutions in water of readily soluble salts. However solutions in other suitable solvent media can be employed as also may suspensions of sparingly soluble salts in water, oil or other inert solvents such as propylene glycol, with or without the addition of soluble or insoluble diluents and/or solid or liquid excipients.

The percentage of active ingredient in the compositions of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. Obviously several unit dosage forms may be administered at about the same time.

The following Example illustrates pharmaceutical preparations according to the invention.

EXAMPLE II

An injectable solution of the formula:

3:3^1 - Diamidinodiphenyl urea dihydrochloride monohydrate	10 g.
Distilled water	up to 100 ml.

was prepared by dissolving the diamidine salt in the distilled water. The solution was filtered and filled into ampoules which were sterilised in an autoclave.

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London, W.C.1.

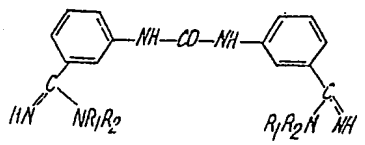
PROVISIONAL SPECIFICATION
No. 28934 A.D. 1959

Improvements in or relating to Diamidines

We, MAY & BAKER LIMITED, a British Company, of Dagenham, Essex, do hereby declare this invention to be described in the following statement:—

This invention relates to new chemical compounds and in particular to new diamidines of therapeutic utility, to processes for their preparation, and to pharmaceutical compositions containing them.

The new diamidines of the present invention are the bases conforming to the general formula:

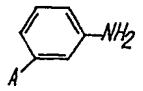


I

and their acid addition salts (wherein R_1 represents a hydrogen atom or a lower alkyl group and R_2 represents a lower alkyl group).

The compounds of general formula I are useful in the treatment of protozoal diseases, especially babesiasis. In this regard it is known that 4 : 4¹ - diamidinophenylurea exhibits slight activity against veterinary trypanosomiasis (Fulton and Yorke, Ann. Trop, med. parasit, 1942, *36*, 131) but it is completely inactive against *B rodhaini* in mice. The high activity of 3,3¹ - diamidinodiphenylurea against *B. rodhaini* in mice and *B. bovis* in calves (as disclosed in our copending Application No. 40428/58) was therefore, completely unexpected. Further research and experimentation has shown that 3,3¹ - di - (*N* - methylamidino)diphenylurea, the preferred compound of the present application has activity comparable with that of 3,3¹ - diamidinodiphenylurea. Furthermore, the compounds of the invention are quick acting and of low toxicity.

According to a feature of the invention, the compounds of general formula I are prepared by a process which comprises the interaction of a compound of the general formula:

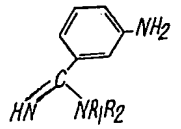


II

(wherein A is a cyano or amidino group of formula —C(:NH)NR_1R_2, where R_1 and R_2 are as hereinbefore defined) or a salt thereof, with phosgene. Where A represents a cyano group, the said cyano group is subsequently converted into an amidino group of formula —C(:NH)NR_1R_2 by known methods.

The reaction is preferably carried out by reacting *m* - aminobenzonitrile with phosgene in the presence of an acid binding agent such as pyridine and in an inert solvent, such as toluene, followed by conversion of the dicyano compound thus obtained into the corresponding diamidine of general formula I by successive treatments with hydrogen chloride and an amine of formula R_1R_2NH (where R_1 and R_2 are as hereinbefore defined).

In another preferred embodiment the reaction is carried out by reacting a salt, such as the hydrochloride, of a *m* - aminobenzamidine of the general formula:



III

(wherein R_1 and R_2 are as hereinbefore defined) with phosgene, either in a basic solvent such as pyridine, or in an inert solvent in the presence of an acid-binding agent such as an alkali metal carbonate, bicarbonate or acetate.

According to a further feature of the invention the compounds of general formula I can be prepared by reaction of a compound of general formula II (wherein A is as previously defined) or a salt thereof with 3,5 - dimethylpyrazole - 1 - carbonamide at an elevated temperature in a hydroxylic solvent such as 2 - ethoxyethanol. Where A represents a cyano group, this cyano group is subsequently converted into an amidino group of formula —C(:NH)NR_1R_2 by known methods.

The compounds of general formula I may also be prepared from the corresponding compounds where R_1 and R_2 represent hydrogen atoms by known methods for the alkylation of amidines, for example, by reaction with alkyl halides, sulphates or toluene - *p* - sulphonates.

In veterinary practice the compounds of the present invention will normally be administered in the form of one of their acid addition salts, it being understood that only those such salts should in practice be employed as contain anions that are relatively innocuous to the animal organism when used in therapeutic doses so that the beneficial physiological properties inherent in the parent compound are not vitiated by side-effects ascribable to those anions. Suitable salts include hydrohalides, for example, hydrochlorides, 8 - chlorotheophyllinates, phosphates, nitrates, sulphates, maleates, fumarates, citrates, tartrates, methane sulphonates and ethane disulphonates.

The following Example illustrates the invention.

EXAMPLE I

m - Aminobenzonitrile (50 g.) in anhydrous pyridine (200 ml.) was treated with a solution of phosgene (15 ml.) in anhydrous toluene (100 ml.) over 10 minutes with mechanical stirring. The red solution was heated for 0.5 hour on the steam bath, cooled, and added to water (2 litres). The pale grey precipitate was filtered off, washed with ether, and crystallised from ethanol (250 ml.). *N*,*N*¹ - Di(*m* - cyanophenyl)urea separated as grey prisms, m.p. 205—206°C.

A suspension of N,N¹ - di(*m* - cyanophenyl)urea (11.6 g.) in anhydrous chloroform (116 ml.), containing anhydrous

ethanol (19.4 ml.) was saturated with anhydrous hydrogen chloride at 0—5°C. After setting aside for 2 hours, a clear solution was obtained, which began to crystallise. After a week, the crystals were filtered off, washed well with anhydrous ether, and dried over calcium chloride. The iminoether hydrochloride so obtained (20 g.) was dissolved in water (200 ml.) and the solution was basified at 0—10°C. with 2N sodium hydroxide. The base which separated was extracted with chloroform, and the chloroform extracts were mixed and dried over anhydrous sodium sulphate. After filtration from the drying agent, the chloroform was distilled off from a bath at 30—35° under reduced pressure. The residual gum (16.9 g.) was dissolved in anhydrous ethanol (200 ml.) and methylamine hydrochloride (6.6 g.) added. The solution was heated at 55—60°C. for 8 hours, and then concentrated under reduced pressure. 3N Hydrochloric acid (300 ml.) was added to the residual gum, and the mixture heated to solution. On cooling, 3,3¹ - di(*N* - methylamidino)diphenylurea dihydrochloride sesquihydrate separated as white needles which decomposed from 210°C., finally melting at 273—274°C.

Similarly prepared were:

3,3¹ - Di(*N* - ethylamidino)diphenylurea dihydrochloride monohydrate, decomposing at 302—305°C.

3,3¹ - Di(*N*,*N*¹ - dimethylamidino)diphenylurea dihydrochloride hydrate, decomposing at 300—302°C.

The present invention includes within its scope pharmaceutical compositions comprising one or more of the compounds of formula I, or an acid addition salt thereof, and a significant amount of a pharmaceutical carrier which may be either a solid material or a liquid. In clinical practice the compounds of the present invention will normally be administered by injection in consequence of which the preferred formulations are those of the kind suitable for parenteral administration.

Preparations for oral ingestion can be liquids or solids or any combination of these forms, such as solutions, suspensions, syrups, elixirs, emulsions, powders or tablets. Pharmaceutical preparations for administration of the active therapeutic agents in unit dose form can take the form of compressed powders (or tablets) or of a powder enclosed in a suitable capsule of absorbable material such as gelatin. These compressed powders (or tablets) can take the form of the active materials mixed with suitable excipients and/or diluents such as starch, lactose, stearic acid, magnesium stearate or dextrin.

In yet a further embodiment, the active material may, as such or in the form of a diluted composition, be put up in powder packets and employed as such.

Preparations for parenteral administration are preferably in the form of sterile solutions in water of readily soluble salts. However solutions in other suitable solvent media can be employed as also may suspensions of sparingly soluble salts in water, oil or other inert solvents such as propylene glycol, with or without the addition of soluble or insoluble diluents and/or solid or liquid excipients.

The percentage of active ingredient in the compositions of the invention may be varied, it being necessary that it should constitute a proportion such that a suitable dosage shall be obtained. Obviously several unit dosage forms may be administered at about the same time.

The following Example illustrates pharmaceutical preparations according to the invention.

EXAMPLE II

An injectable solution of the formula:

3,3¹ - Di(N - methylamidino)diphenylurea dihydrochloride sesquihydrate	10 g.
Distilled water	up to 100 ml.

was prepared by dissolving the diamidine salt in the distilled water. The solution was filtered and filled into ampoules which were sterilised in an autoclave.

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